

## 1. TITLE PAGE

### CLINICAL TRIAL PROTOCOL

**RANDOMIZED, CONTROLLED, OPEN AND UNICENTRIC PHASE II CLINICAL TRIAL, WITH  
TWO PARALLEL GROUPS, TO EVALUATE THE ANTIDEPRESSANT EFFICACY OF  
PSYCHOTHERAPY AND CITALOPRAM IN WOMEN DIAGNOSED WITH BREAST CANCER  
AND MAJOR DEPRESSION.  
CAMAD PROJECT**

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| <b>Name of Sponsor:</b><br>Dr. Cinto Segalàs  | CLINICAL TRIAL – CAMAD |
| <b>TITLE OF THE STUDY:</b> Randomized, controlled, open and unicentric phase II clinical trial, with two parallel groups, to evaluate the antidepressant efficacy of psychotherapy and citalopram in women diagnosed with breast cancer and major depression. CAMAD project.  |                        |
| <p><b>BACKGROUND:</b></p> <p>Breast Cancer (BC) is the most common malignant tumor in women. And although it has a high survival rate, 25% of patients with BC will suffer from major depression (MD) (1). The appearance of depressive symptoms in patients with BC occurs mainly in the first year after diagnosis and is associated with a global increase in cancer mortality, as well as worse tolerance and adherence to antineoplastic treatments, worsening the course and prognosis of oncological disease (2,3).</p> <p>Within the therapeutic approaches for the treatment of depression we have psychopharmacological and psychotherapeutic strategies. The use of psychotropic drugs compared to placebo has been shown to be beneficial, although its main limitation is the interaction with some antineoplastic drugs administered in the treatment of BC and the reduction of their antitumor efficacy (4). Positive Psychotherapy in Cancer (PPC) is a cognitive-behavioral and humanistic-existential treatment that has proven to be effective in the treatment of depression in BC and does not present, unlike the use of psychotropic drugs, pharmacological interactions or secondary effects (5). Despite this, there are no randomized controlled clinical trials that compare antidepressant efficacy between drug use vs CPP in MD in BC.</p> <p>Biases in emotional processing have been extensively studied in Major Depressive Disorder (MDD), for example by using the Backward Masking Test (BMT) -which assesses the emotional recognition of facial expression-, it has been observed that patients Clinically depressed in relation to healthy subjects, are more sensitive to information with negative emotional charge (faces that express sadness), with respect to neutral (faces that do not express emotions) and positive (faces that show joy)(6). Alterations in emotional processing in depressed patients, measured with neuropsychological tests, have been associated with changes in functional neuroimaging in specific regions such as the amygdala and the pregenual anterior cingulate cortex (pACC). Thus, depressed patients present greater activation of both regions in the face of negative stimuli compared to healthy controls, and in the case of pACC this association translates into a reduction in depressive symptoms in response to the psychopharmacological treatment tested, granting cognitive biases and neuroimaging findings a possible role as predictors of response to drug treatment in MDD (7,8). The study of specific biomarkers that allow knowing in advance the degree of clinical response to a specific therapeutic strategy in the treatment of depression in BC is of vital importance to be able to design increasingly personalized and effective treatments in order to improve both the course and the prognosis of depression and oncological disease.</p> <p>The 'CAMAD project' aims to provide evidence based on two clinical trials:</p> <ol style="list-style-type: none"> <li>1) the first clinical trial of this project is a pilot, feasibility, single-center, randomized clinical trial, in parallel groups of the therapeutic strategies used in our center; and</li> <li>2) the second clinical trial of this project is a phase III, multicenter, randomized, parallel group clinical trial.</li> </ol> <p>Therefore, the pilot clinical trial at hand is the previous step for the second clinical trial of the CAMAD project. Its objective is to provide the first evidence on the viability and antidepressant efficacy of pharmacological treatment (citalopram) and treatment with psychotherapy in a group of patients with BC and MD."</p> |                        |
| <p><b>OBJECTIVES</b></p> <p><b>Primary Objective:</b></p> <ul style="list-style-type: none"> <li>○ To provide evidence on the viability of the clinical trial and on the antidepressant efficacy of pharmacological treatment (citalopram) and treatment with psychotherapy in a group of patients with BC and MD.</li> </ul> <p><b>Secondary Objectives:</b></p> <p><u>Clinical objectives:</u></p> <ul style="list-style-type: none"> <li>○ To evaluate the antidepressant effect of the therapeutic strategies studied and their impact on quality of life.</li> </ul>   |                        |

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| <ul style="list-style-type: none"> <li>○ To evaluate the antidepressant effect of the therapeutic strategies studied and their impact on socio-labor adaptation.</li> <li>○ To estimate which clinical, sociodemographic and oncospecific treatment variables predict a greater antidepressant response to a specific treatment strategy.</li> </ul> <p><u>Clinical objectives - biomarkers</u></p> <ul style="list-style-type: none"> <li>○ To study possible biomarkers of functional neuroimaging and emotional processing specific to MD in BC that could allow predicting the response to a given therapeutic strategy.</li> </ul> <p><u>Safety Objectives</u></p> <ul style="list-style-type: none"> <li>○ To evaluate the safety (12 weeks) of the two therapeutic strategies studied: pharmacological treatment (citalopram) and treatment with psychotherapy.</li> </ul> <p><u>Pharmaco-economic Objectives</u></p> <ul style="list-style-type: none"> <li>○ To estimate the cost-effectiveness of pharmacological treatment with citalopram with respect to psychological treatment in patients in our environment with BC and MD, as well as its economic impact on return to work.</li> </ul>   |                        |
| <p><b>STUDY DESIGN:</b></p> <p>A randomized, controlled, open and unicentric phase II clinical trial, with two parallel groups, to evaluate the antidepressant efficacy of psychotherapy and citalopram in women diagnosed with breast cancer and major depression.</p> <p>The patients included in the clinical trial will be treated with citalopram 20-40 mg / 24 hours (recommended dose in the technical sheet: <a href="https://cima.aemps.es/cima/dochtml/ft/60884/FT_60884.html">https://cima.aemps.es/cima/dochtml/ft/60884/FT_60884.html</a>) or with psychotherapy [protocol implemented in the clinical practice of the ICO (Institut Català d'Oncologia) -Bellvitge].</p> <p>Visits: There will be a total of 13 visits in this clinical trial. A first in-person inclusion visit and 12 subsequent online follow-up appointments with weekly frequency (which coincides in number and procedure with the visits made in our clinical practice in patients undergoing psychological treatment) to all patients regardless of the group to which they have been randomized.</p> <p><b>Visit 1 (baseline visit, patient inclusion):</b></p> <p>The patient will be informed about the study and will be given the information sheet and the informed consent for her signature.</p> <p>Once the informed consent has been signed, the clinical evaluation will be carried out and it will be confirmed that the patient meets the inclusion criteria and none of the exclusion criteria. The sociodemographic, clinical and laboratory data (hemogram / biochemistry) of the clinical history will be recorded. A battery of scales will be administered that collect the intensity of symptoms of anxiety and depression, quality of life, global clinical severity, social support, pain, fatigue and work adaptation.</p> <p>In the case of obtaining the necessary financing for the project, in addition to the previously mentioned tests, a functional magnetic resonance imaging (fMRI) will be scheduled and simultaneously an emotional processing task will be carried out to evaluate possible emotional biases (BMT) before the treatment starts. If resources were not obtained to carry out the study of image and emotional processing through the BMT, the Dote Probe Test (DPT) would be performed, which assesses emotional biases.</p> <p>Battery of scales to evaluate:</p> <ol style="list-style-type: none"> <li>1. Hospital Anxiety and Depression Scale (HADS): self-applied measure of severity of anxiety and depressive symptoms.</li> <li>2. Beck Depression Inventory (BDI): self-applied measure of severity of depressive symptoms.</li> <li>3. Clinical Global Impression (CGI): measure of global clinical severity.</li> <li>4. European Quality of Life Scale (EQ-5D-3L): measure of quality of life.</li> </ol> |                        |

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| <ol style="list-style-type: none"> <li>5. Medical Outcomes Study -Social Support Survey (MOS-SSS): measure of perceived social support.</li> <li>6. Work adaptation (days off).</li> <li>7. Visual analog scale to measure pain.</li> <li>8. Visual analog scale to measure fatigue.</li> <li>9. Pharmacological adherence (SMAQ): a measure of pharmacological adherence.</li> <li>10. Side effects scale (UKU): measure of side effects derived from the consumption of psychotropic drugs.</li> <li>11. Extreme Life Events Inventory (ELEI): self-applied measure of traumatic events and their impact on the life course.</li> <li>12. Rosenberg Self-Esteem Scale (RSES): self-applied measure of self-esteem (implicit and explicit).</li> </ol>                     |                        |
| <b>Start of treatment (day 0):</b><br>Once the fMRI and the BMT have been performed, the patients will be given indications to start treatment, whether pharmacological or psychological. The day of this first visit is considered day 0 or the day of the start of treatment (First intake of citalopram or first psychotherapy session).   |                        |
| <b>Visit 2 (7 (1 week) ± 2 days after starting treatment -day 0-):</b><br>Routine control visit in which an assessment of the general condition will be carried out and it will be verified and recorded that the patient performs correctly the pharmacological treatment or psychotherapy, in addition to evaluating her safety.  |                        |
| <b>Visit 3 (at 14 (2 weeks) ± 2 days after starting treatment -day 0-):</b><br>Routine control visit in which an assessment of the general condition will be carried out and it will be verified and recorded that the patient performs correctly the pharmacological treatment or psychotherapy, in addition to evaluating her safety.   |                        |
| <b>Visit 4 (at 21 (3 weeks) ± 2 days after starting treatment -day 0-):</b><br>It will be verified and recorded that each patient, depending on the group, performs correctly the pharmacological treatment or psychotherapy.<br>Tolerance and adherence to treatment with citalopram will be studied in the pharmacological treatment branch.<br>Changes in cancer-specific treatment will be recorded.  |                        |
| The following battery of scales will be administered: <ol style="list-style-type: none"> <li>1. Hospital Anxiety and Depression Scale (HADS): self-applied measure of severity of anxiety and depressive symptoms.</li> <li>2. Beck Depression Inventory (BDI): self-applied measure of severity of depressive symptoms.</li> <li>3. Clinical Global Impression (CGI): measure of global clinical severity.</li> <li>4. Work adaptation (days off).</li> <li>5. Visual analog scale to measure pain.</li> <li>6. Visual analog scale to measure fatigue.</li> <li>7. Pharmacological adherence (SMAQ): a measure of pharmacological adherence.</li> <li>8. Side effects scale (UKU): measure of side effects derived from the consumption of psychotropic drugs.</li> </ol> |                        |
| <b>Visit 5 (at 28 (4 weeks) ± 2 days after starting treatment -day 0-):</b><br>Routine control visit in which an assessment of the general condition will be carried out and it will be verified and recorded that the patient performs correctly the pharmacological treatment or psychotherapy, in addition to evaluating her safety.   |                        |
| <b>Visit 6 (35 (5 weeks) ± 2 days after starting treatment -day 0-):</b><br>Routine control visit in which an assessment of the general condition will be carried out and it will be verified and recorded that the patient performs correctly the pharmacological treatment or psychotherapy, in addition to evaluating her safety.  |                        |
| <b>Visit 7 (42 (6 weeks) ±2 days after starting treatment –day 0-):</b><br>It will be verified and recorded that each patient, depending on the group, performs correctly the pharmacological treatment or psychotherapy.   |                        |

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| <p>Tolerance and adherence to treatment with citalopram will be studied in the pharmacological treatment branch. Changes in cancer-specific treatment will be recorded.</p> <p>The following battery of scales will be administered:</p> <ol style="list-style-type: none"> <li>1. Hospital Anxiety and Depression Scale (HADS): self-applied measure of severity of anxiety and depressive symptoms.</li> <li>2. Beck Depression Inventory (BDI): self-applied measure of severity of depressive symptoms.</li> <li>3. Clinical Global Impression (CGI): measure of global clinical severity.</li> <li>4. Work adaptation (days off).</li> <li>5. Visual analog scale to measure pain.</li> <li>6. Visual analog scale to measure fatigue.</li> <li>7. Pharmacological adherence (SMAQ): a measure of pharmacological adherence.</li> <li>8. Side effects scale (UKU): measure of side effects derived from the consumption of psychotropic drugs.</li> </ol> <p><b>Visit 8 (49 (7 weeks) ±2 days after starting treatment -day 0-):</b></p> <p>Routine control visit in which an assessment of the general condition will be carried out and it will be verified and recorded that the patient performs correctly the pharmacological treatment or psychotherapy, in addition to evaluating her safety.</p> <p><b>Visit 9 (56 (8 weeks) ±2 days after starting treatment -day 0-):</b></p> <p>Routine control visit in which an assessment of the general condition will be carried out and it will be verified and recorded that the patient performs correctly the pharmacological treatment or psychotherapy, in addition to evaluating her safety.</p> <p><b>Visit 10 (63 (9 weeks) ±2 days after starting treatment -day 0-):</b></p> <p>It will be verified and recorded that each patient, depending on the group, performs correctly the pharmacological treatment or psychotherapy.</p> <p>Tolerance and adherence to treatment with citalopram will be studied in the pharmacological treatment branch. Changes in cancer-specific treatment will be recorded.</p> <p>The following battery of scales will be administered:</p> <ol style="list-style-type: none"> <li>1. Hospital Anxiety and Depression Scale (HADS): self-applied measure of severity of anxiety and depressive symptoms.</li> <li>2. Beck Depression Inventory (BDI): self-applied measure of severity of depressive symptoms.</li> <li>3. Clinical Global Impression (CGI): measure of global clinical severity.</li> <li>4. Work adaptation (days off).</li> <li>5. Visual analog scale to measure pain.</li> <li>6. Visual analog scale to measure fatigue.</li> <li>7. Pharmacological adherence (SMAQ): a measure of pharmacological adherence.</li> <li>8. Side effects scale (UKU): measure of side effects derived from the consumption of psychotropic drugs.</li> </ol> <p><b>Visit 11 (70 (10 weeks) ±2 days after starting treatment -day 0-):</b></p> <p>Routine control visit in which an assessment of the general condition will be carried out and it will be verified and recorded that the patient performs correctly the pharmacological treatment or psychotherapy, in addition to evaluating her safety.</p> <p><b>Visit 12 (77 (11 weeks) ±2 days after starting treatment -day 0-):</b></p> <p>Routine control visit in which an assessment of the general condition will be carried out and it will be verified and recorded that the patient performs correctly the pharmacological treatment or psychotherapy, in addition to evaluating her safety.</p> <p><b>Visit 13 or end of study visit (84 (12 weeks) ±4 days after starting treatment -día 0-):</b></p> <p>It will be verified and recorded that each patient, depending on the group, performs correctly the pharmacological treatment or psychotherapy.</p> |                        |

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| <p><b>METHODS:</b></p> <p><b>STUDY POPULATION:</b></p> <p>The target population of this clinical trial is made up of female patients diagnosed with BC who, during the first year after the diagnosis of oncological disease, present affective symptoms that meet DSM-V criteria for MD.</p> <p>Patients will be recruited from a screening program (score &gt; 7 on the Hospital Depression and Anxiety Scale, HADS) for emotional distress included in an online psychosocial care protocol that is offered to all patients diagnosed with BC and who receive treatment at the Catalan Institute of Oncology (ICO) -Bellvitge.</p> <p>Study patients will be recruited from the ICO-Bellvitge psycho-oncology service if they meet the inclusion criteria and there is no reason for exclusion indicated below:</p> <p><b>Inclusion Criteria:</b></p> <ol style="list-style-type: none"> <li>1. Female patients first time diagnosed with BC (stage I, II, III or IV) between 18 and 75 years (both inclusive).</li> <li>2. Patients with a “moderate-severe” level of emotional distress who meet the diagnostic criteria for major depression for at least two weeks or adjustment disorder with depressive mood for at least two months, according to DSM-V criteria, during the twelve months following the diagnosis of BC.</li> <li>3. Signature of the informed consent.</li> </ol> <p><b>Exclusion Criteria:</b></p> <ol style="list-style-type: none"> <li>1. Women who are pregnant or breastfeeding.</li> <li>2. Suicidal risk.</li> <li>3. Metastatic brain disease.</li> <li>4. Personal History of oncological disease.</li> <li>5. Personal History of serious somatic disease (cardiac, hepatic, respiratory, endocrinological, neurological, and hematological).</li> <li>6. Personal History of organic brain disorder, substance abuse / dependence.</li> <li>7. Personal History of psychotic disorder, bipolar disorder and / or mental retardation.</li> <li>8. Contraindications of citalopram treatment.</li> <li>9. Taking antidepressants after the BC diagnosis.</li> <li>10. Psychotherapy treatment after BC diagnosis.</li> </ol> |                        |
| <p><b>EVALUATION CRITERIA:</b></p>   |                        |

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| <p><b>Main criterion (for the main objective):</b><br/> <u>Antidepressant efficacy</u></p> <ul style="list-style-type: none"> <li>○ Score on the BDI scale.</li> </ul> <p><b>Secondary criteria (for secondary objectives):</b></p> <p><u>Antidepressant efficacy</u></p> <ul style="list-style-type: none"> <li>○ Score on the EQ-5D-3L quality of life questionnaire.</li> <li>○ Socio-labor adaptation: number of days off work</li> </ul> <p><b>* Predictive factors</b><br/>         or sociodemographic variables<br/>         or quality of life and social adaptation at the time of diagnosis<br/>         or clinical variables: stage of oncological disease, cancer-specific treatment (surgery, radiotherapy, chemotherapy and / or hormone therapy)<br/>         or psychosocial support<br/>         or traumatic events<br/>         or self esteem</p> <p><u>Biomarkers</u></p> <ul style="list-style-type: none"> <li>○ Functional neuroimaging (with fMRI the activity of certain brain structures such as pACC will be evaluated) and emotional processing with BMT: Response predictors.</li> </ul> <p>Note: The secondary criterion based on biomarkers can only be performed if the study manages to obtain funds for the performance of such neuroimaging and emotional processing tests.</p> <p><u>Safety:</u></p> <ul style="list-style-type: none"> <li>○ Measurement of side effects derived from the consumption of psychotropic drugs.</li> <li>○ Total number of adverse events by treatment arm.</li> <li>○ Number of adverse events related to the treatments under study.</li> </ul> |                        |
| <p><b>DURATION OF THE CLINICAL TRIAL:</b><br/>         The clinical trial is expected to begin in September of 2021.<br/>         The recruitment of the 40 patients is expected to take 12 months.<br/>         Patients will be followed up to 84 (12 weeks) ± 4 days after starting treatment.<br/>         After the clinical phase, 3 months are required to clean the data and perform the statistical analyzes.<br/>         The final report will be available in nine months from the completion of the statistical analyzes.<br/>         The expected completion date (final report) is September of 2023</p>   |                        |
| <p><b>DETERMINING SAMPLE SIZE:</b><br/>         No formal calculation of the sample size has been made because it is a pilot clinical trial, that is, an exploratory feasibility study.<br/>         A total of 40 consecutive patients who meet the inclusion / exclusion criteria will be studied: 20 patients in the pharmacological treatment group (citalopram) and 20 patients in the psychotherapy treatment group.</p>   |                        |
| <p><b>STATISTICAL CONSIDERATIONS:</b><br/> <u>Definitions:</u><br/>         Responder 1: ≥50% reduction in BDI at the end of study visit compared to the baseline score (study start visit) will be considered responders.</p> <p>Other definitions of responder:<br/>         Respondent 2: ≥50% reduction in BDI at some point in the study from baseline (baseline visit).</p>  |                        |

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| <p>Respondent 3: <math>\geq 30\%</math> reduction in BDI at the end of study visit compared to the baseline score (start of study visit).<br/>         Respondent 4: <math>\geq 30\%</math> reduction in BDI at some point in the study from baseline (baseline visit).</p> <p><u>Descriptive analysis:</u><br/>         A descriptive analysis of the baseline sociodemographic and clinical profile of the patients included in the study as a whole and by study groups will be carried out.</p> <p><u>Efficacy analysis:</u><br/> <i>Main analysis:</i> The main objective of the study will be evaluated by an analysis of covariance. The level of depression of the patients will be evaluated using the BDI questionnaire at the end of study visit (EoC), it will be the dependent variable and the independent variables will be the study group and the level of depression of the patients evaluated using the BDI questionnaire at the baseline visit. Tables will be presented with the coefficients of the model and its 95% confidence interval. In addition, the effect size will be mediated by presenting the marginal means per study group and their standardized difference together with their 95% confidence intervals.</p> <p>Secondary analysis. The main analysis will be replicated in an adjusted way, evaluating the role of sociodemographic factors, quality of life and baseline social adaptation, clinical variables of oncological disease and psychosocial support.</p> <p>The main analysis will be replicated in a crude and adjusted way using the EQ-5D-3L questionnaire. Socio-labor adaptation will be evaluated by comparing the number of days off work between study groups using the Wilcoxon test. If the variable is distributed as a Poisson or a negative Binomial, a generalized linear model will be estimated in order to be able to compare in an adjusted way the socio-occupational adaptation of the patients between study groups.</p> <p>Using generalized mixed models, the evolution throughout the visits of the different response variables (BDI and EQ-5D-3L) will be analyzed, taking the patient as a cluster. The dependent variable of each model will be the respective response variable measured throughout the visits and the independent variables will be the random constant, the visit, the study group, the baseline value of the dependent variable and the interaction between the visit and the study group. The significance of the interaction will be assessed and the marginal means of each group in each visit estimated by the model will be graphically presented. Likewise, the estimated model will be replicated, adjusting for sociodemographic factors, quality of life and baseline social adaptation, clinical variables of the oncological disease and psychosocial support.</p> <p>The RMf and BMT results will be pre-processed using the SPM program (Statistical Parametric Mapping, <a href="https://www.fil.ion.ucl.ac.uk/spm/software/">https://www.fil.ion.ucl.ac.uk/spm/software/</a>). Subsequently, the prediction analysis will be carried out to establish which biomarkers have a value as predictors of response to antidepressant treatment in patients with BC and MD. In case of not obtaining financing, predictive analysis will be carried out only for the DPT.</p> <p><u>Security analysis:</u><br/>         A descriptive analysis of the adverse events recorded throughout the trial of the patients included in the population will be carried out for safety as a whole and by study groups.</p> <p>The application conditions of all the estimated models will be evaluated. The program that will be used to perform the statistical analysis will be R version 3.6 or higher.</p> |                        |
| <p><b>BIBLIOGRAPHY:</b></p> <ol style="list-style-type: none"> <li>1- Fann JR, Thomas-Rich AM, Katon WJ, Cowley D, Pepping M, McGregor BA, Gralow J. Major depression after breast cancer: a review of epidemiology and treatment. <i>Gen Hosp Psychiatry</i>. 2008 Mar-Apr;30(2):112-26.</li> <li>2- Vodermaier A, Linden W, Rnic K, Young SN, Ng A, Ditsch N, Olson R. Prospective associations of depression with survival: a population-based cohort study in patients with newly diagnosed breast cancer. <i>Breast Cancer Res Treat</i>. 2014 Jan;143(2):373-84.</li> <li>3- Avis NE, Levine B, Naughton MJ, Case LD, Naftalis E, Van Zee KJ. Age-related longitudinal changes in depressive symptoms following breast cancer diagnosis and treatment. <i>Breast Cancer Res Treat</i>. 2013 May;139(1):199-206.</li> </ol>   |                        |

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| <ul style="list-style-type: none"><li>4- Miguel C, Albuquerque E. Drug interaction in psycho-oncology: antidepressants and antineoplastics. <i>Pharmacology</i>. 2011;88(5-6):333-9.22</li><li>5- Ochoa, C., &amp; Casellas-Grau, A. (2015). Positive Psychotherapy in Cancer: Facilitating Posttraumatic Growth in Assimilation and Accomodation of Traumatic Experience. In C.R. Martin, V. R. Preedy &amp; B. P.Vinood (Eds.). <i>Comprehensive Guide to Post-Traumatic Stress Disorder</i> (pp.113-127). Verna: Springer International Publishing Switzerland.</li><li>6- Victor TA, Furey ML, Fromm SJ, Ohman A, Drevets WC. Relationship between amygdala responses to masked faces and mood state and treatment in major depressive disorder. <i>Arch Gen Psychiatry</i>. 2010 Nov;67(11):1128-38.</li><li>7- Victor TA, Furey ML, Fromm SJ, Öhman A, Drevets WC. Changes in the neural correlates of implicit emotional face processing during antidepressant treatment in major depressive disorder. <i>Int J Neuropsychopharmacol</i>. 2013 Nov;16(10):2195-208.</li><li>8- Godlewska BR, Browning M, Norbury R, Igoumenou A, Cowen PJ, Harmer CJ. Predicting Treatment Response in Depression: The Role of Anterior Cingulate Cortex. <i>Int J Neuropsychopharmacol</i>. 2018 Nov 1;21(11):988-996.5</li></ul> |                        |